National Institute of Neurological Disorders and Stroke

NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

NINDS StrokeNet Update

Platform Trials of Thrombectomy in Acute Stroke (OTA) Program

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DCR/NINDS

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NDMC

Sept 16, 2022

http://nihstrokenet.org/

How did we get here?

Domain

EVT Indication Expansion → *e.g., EVT for low NIHSS, large core, children, etc…*

Novel / Improved Concomitant Therapy to EVT → *e.g., BP control, avoiding tPA, general anesthesia or sedation, novel neuroprotective agents, etc…*

Technol / Systems Improve Access to EVT → *e.g., prehospital identification for EVT routing, etc…*

Deluge of EVT Proposals to NINDS

Following the lead from the FDA

Master Protocols

FDA's Woodcock: The Clinical Trials System is 'Broken'

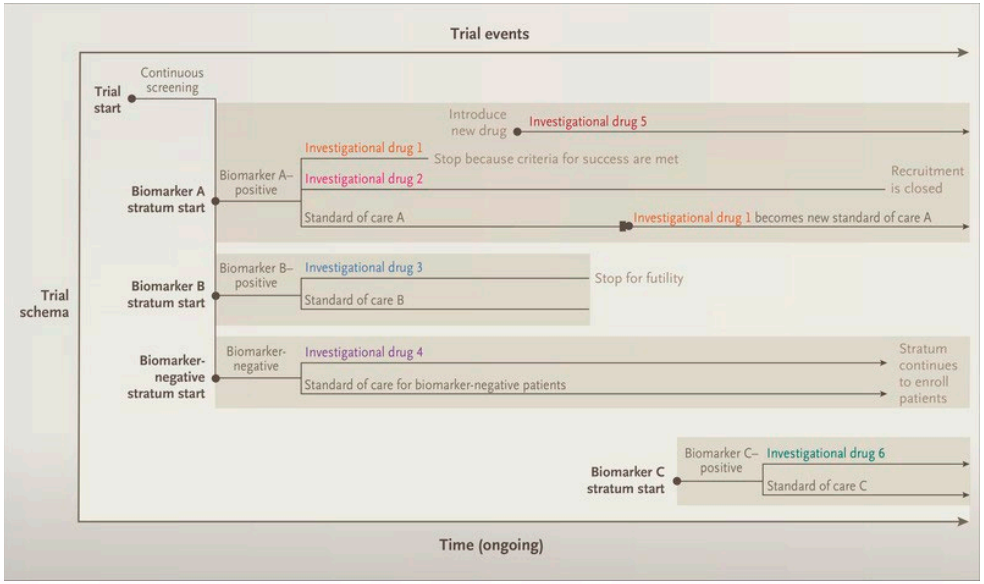
Posted 20 September 2017

The clinical trials system is "broken" and there needs to be new ways to collect and utilize patient data, Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, told a workshop on real world evidence (RWE) at the National Academies of Sciences, Engineering, and Medicine on Wednesday.

The comment came at the end of Woodcock's talk in which she also noted that use of master protocols (ie. protocols for trials that look at multiple therapies in a single disease or a single treatment in multiple diseases) and the development of new clinical trial networks "need to be the future."

Essential features of a platform

- Able to compare multiple interventions (arms)
- Examine effects across subgroups of patients with distinct but related clinical features
- Minimize downtime between trials
- Share control groups
- Drop arms early when treatments fail
- Combine promising treatment arms
- Share resources



Other Transactional Authorities (OTAs)

What is it?

- Unique type of legal funding instrument **other than** a contract, grant, or cooperative agreement
- NIH requires authority to enter into an OT and must differentiate OTs from existing grants/ contracts
- Requirements for awards issued under OTAs are generally included in the authorizing language or budgetary appropriation for such awards
- One reason for using an OTA may be:
  - Seeking participation from nontraditional research partners (e.g., pharmaceutical companies, patient advocacy organizations)
- Able to mitigate high risk objectives because OTAs give ability to terminate award if milestones are not met

Research Opportunity Announcements

A Research Opportunity Announcement (ROA) is a public document that announces the availability of an Other Transaction (OT). It provides the initiative's purpose, type of award, instructions on how to apply, due date for proposals or applications, and research opportunity number.

Platform Trials of Thrombectomy in Acute Stroke (OT2)	OTA-22-001	NINDS is interested in establishing master protocols to enable platform trials in thrombectomy in acute stroke using a seamless rolling approach to be conducted within the existing NIH StrokeNet infrastructure. Trials that further refine patient groups that do or do not benefit from mechanical thrombectomy, and using which management approaches, will also open the door to testing neuroprotectant strategies in an efficient, timely, and cost-effective manner. This ROA will establish the groundwork to include the master protocol for platform trials with the NIH StrokeNet.	StrokeNET	Scott Janis, PhD

OTA initiated with StrokeNet on Sept 1, 2022

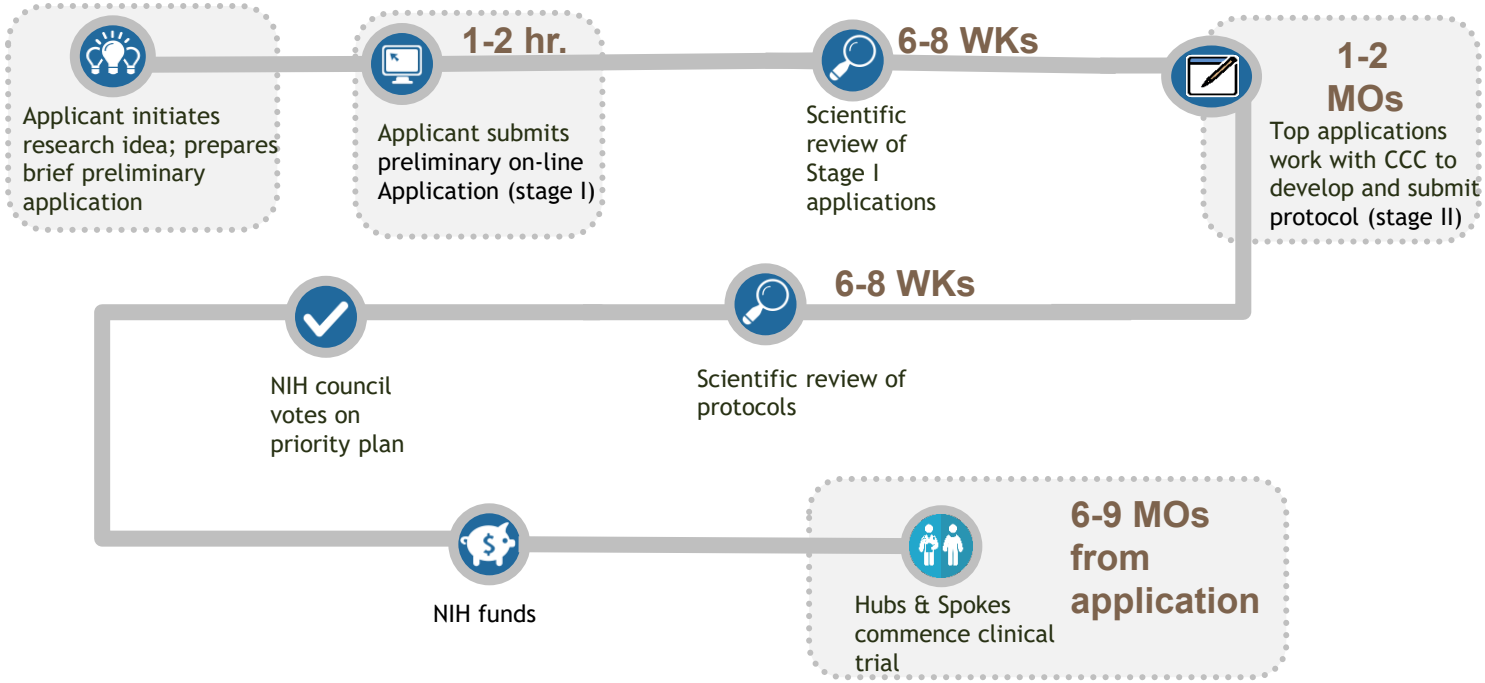
Plans going forward
Research Opportunity Announcements

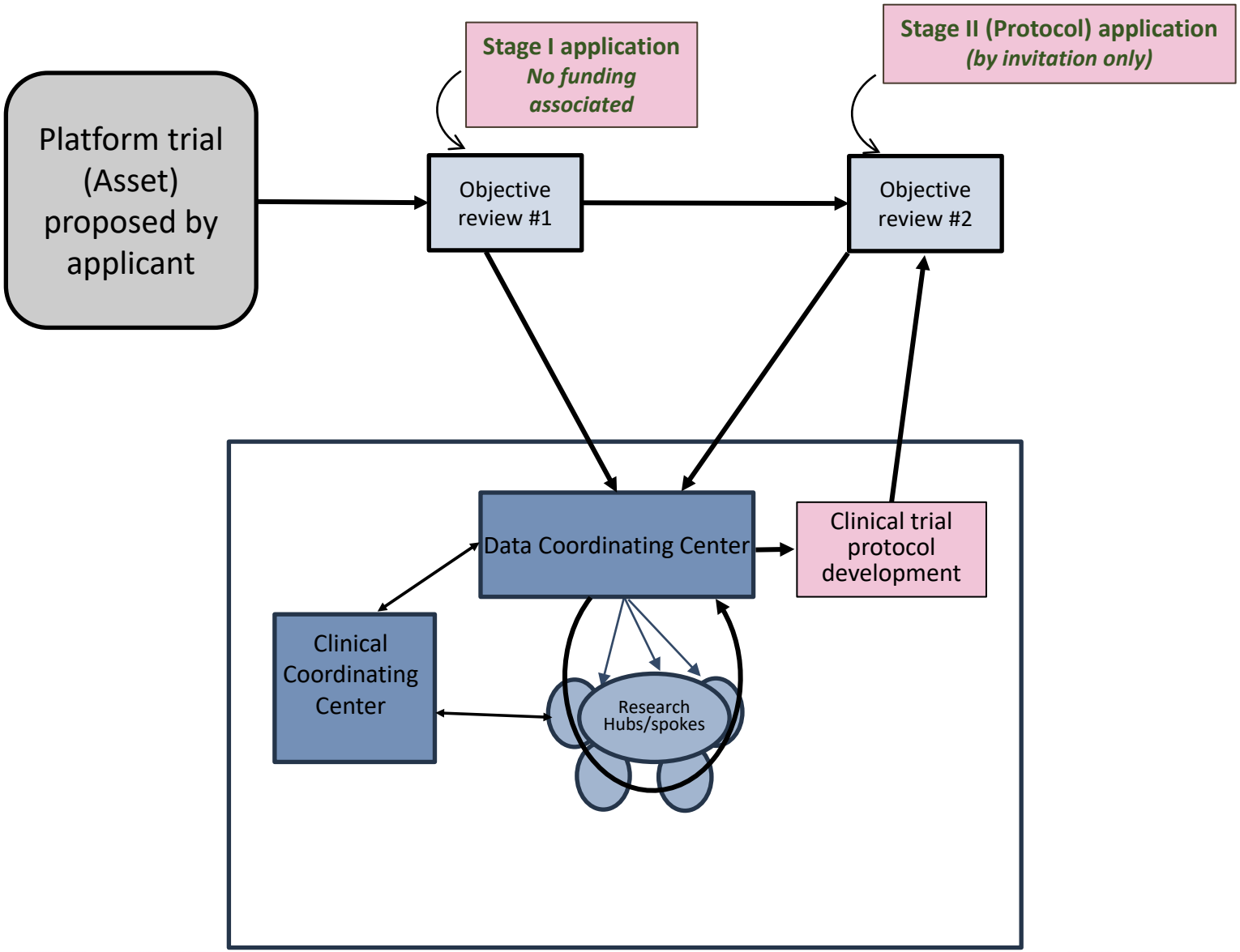
Expecting a set of ROA's that will allow the full build-out of the platform and a mechanism for accepting platform trial proposals

Expected timeline is early next year

ROA's and instructions will be published on the NINDS website:
https://www.ninds.nih.gov/funding/find-funding-opportunities/research-opportunity-announcements?search-term=OTA

How the Application & Review Process will work




Platform trial (Asset) proposed by applicant
Stage I application
No funding associated
Objective review #1
Stage II (Protocol) application
(by invitation only)
Objective review #2
Data Coordinating Center
Clinical trial protocol development
Clinical Coordinating Center
Research Hubs/spokes

Brief Overview

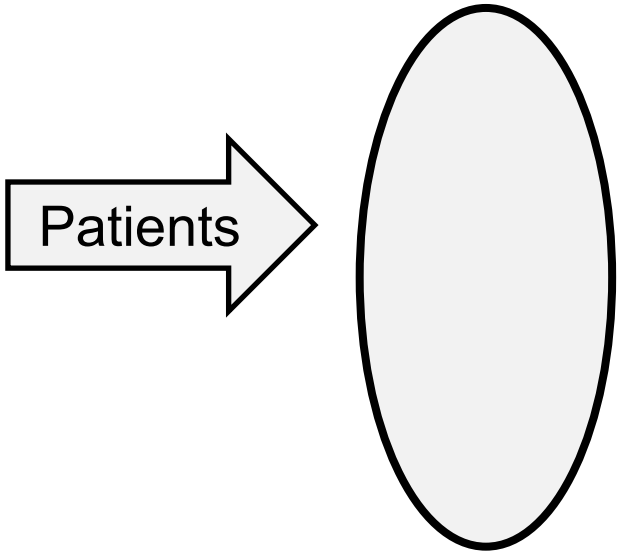
StrokeNet Thrombectomy Platform (STEP) Trial Design

- *Eva Mistry, MBBS, MSCI, FAHA*
- *Jordan Elm, PhD*
- *On behalf of STEP Executive Committee*

StrokeNet Thrombectomy Platform (STEP)

- Randomized Multifactorial Adaptive Platform (REMAP design)
- Leverages existing registries for data collection

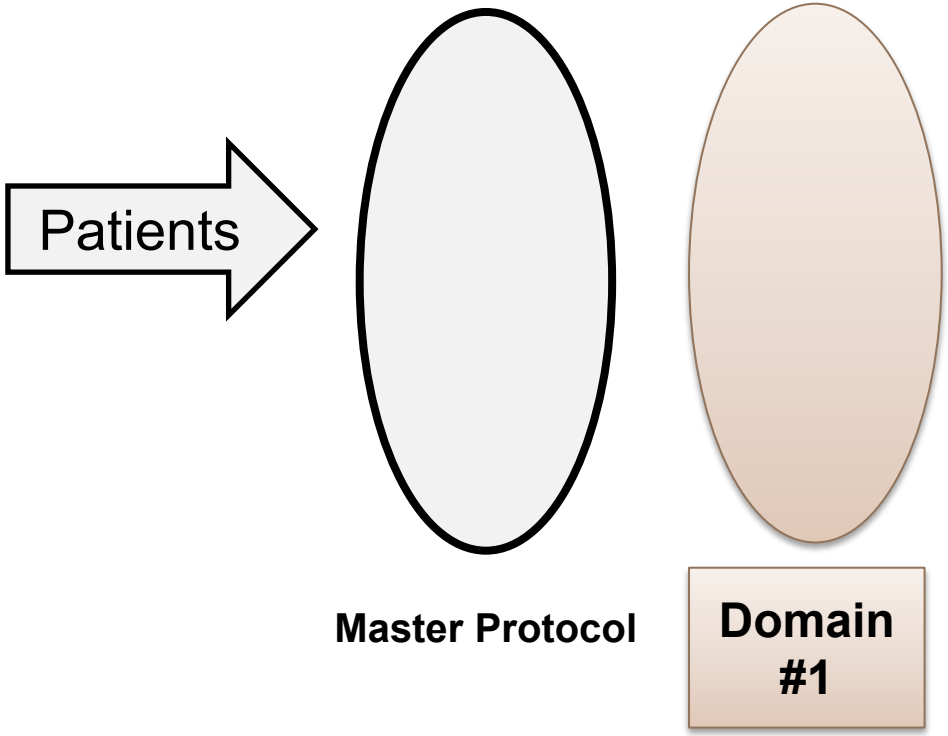
STEP- Master Protocol



Master Protocol

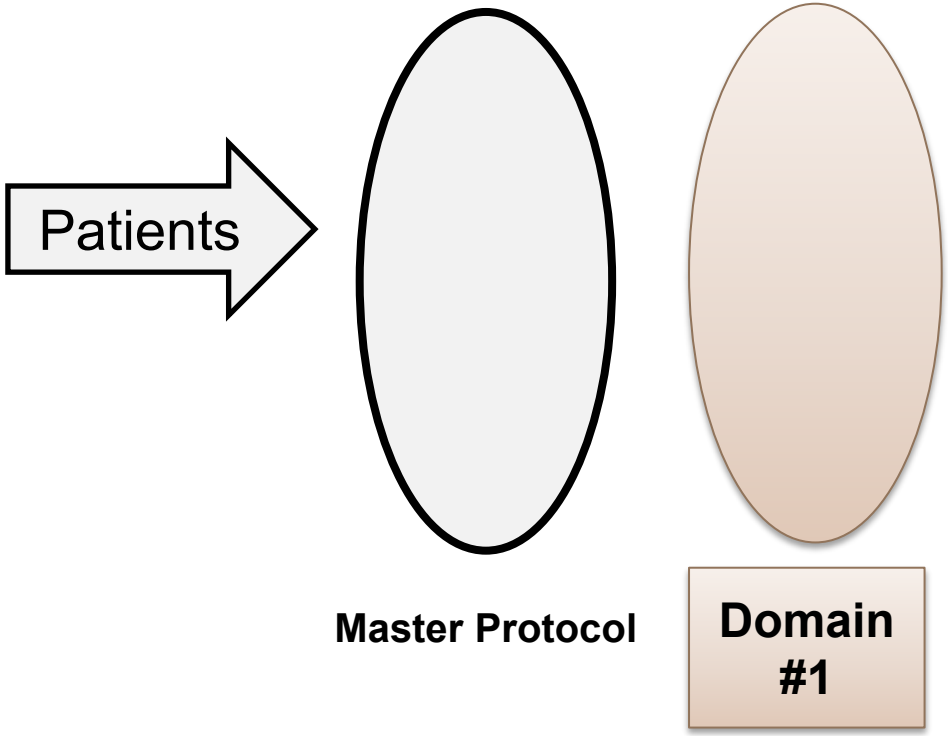
- Defines the largest Set of Inclusion/Exclusion Criteria to be studied
  - All acute ischemic stroke patients with a large or medium vessel occlusion
- Broadly defines overall study terminology and procedures
  - Domain specific appendices are referred to for domain specific details
- Specifies a single underlying statistical model

STEP- Domains



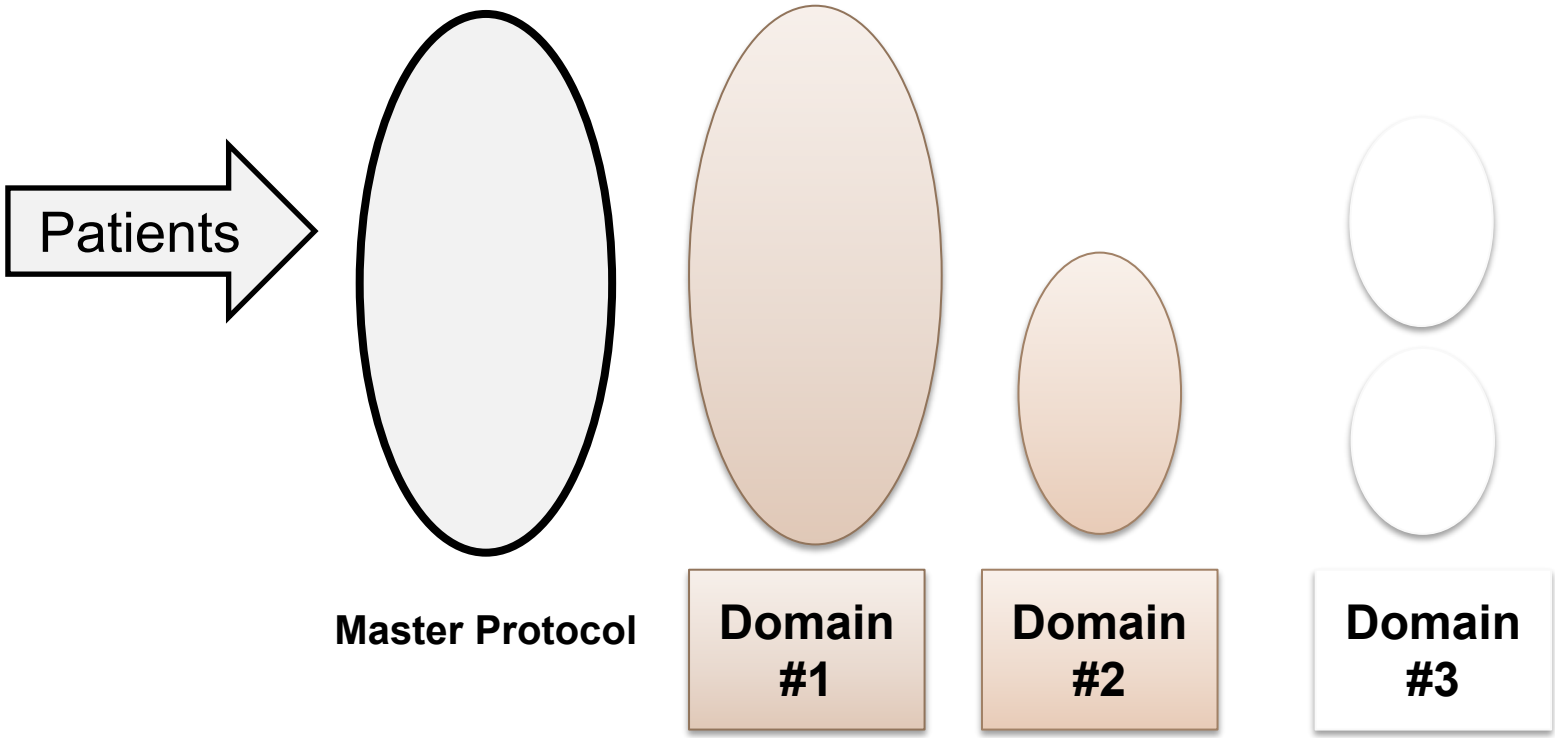
- Studies of **mutually exclusive** interventions
  - EVT vs MM
  - Neuroprotectant 1 vs Neuroprotectant 2 vs control
- Patients can be randomized within multiple domains (**multifactorial**)

STEP- Domain Specific Appendix



- Defines a set of patients eligible for the domain
  - Must be subset of platform trial I/E population
- Details the type/delivery of intervention(s)
- Defines the rules for **randomization**
- Defines the analysis methods, **adaptations**
- May define how it works with other domains (co-enrollment)

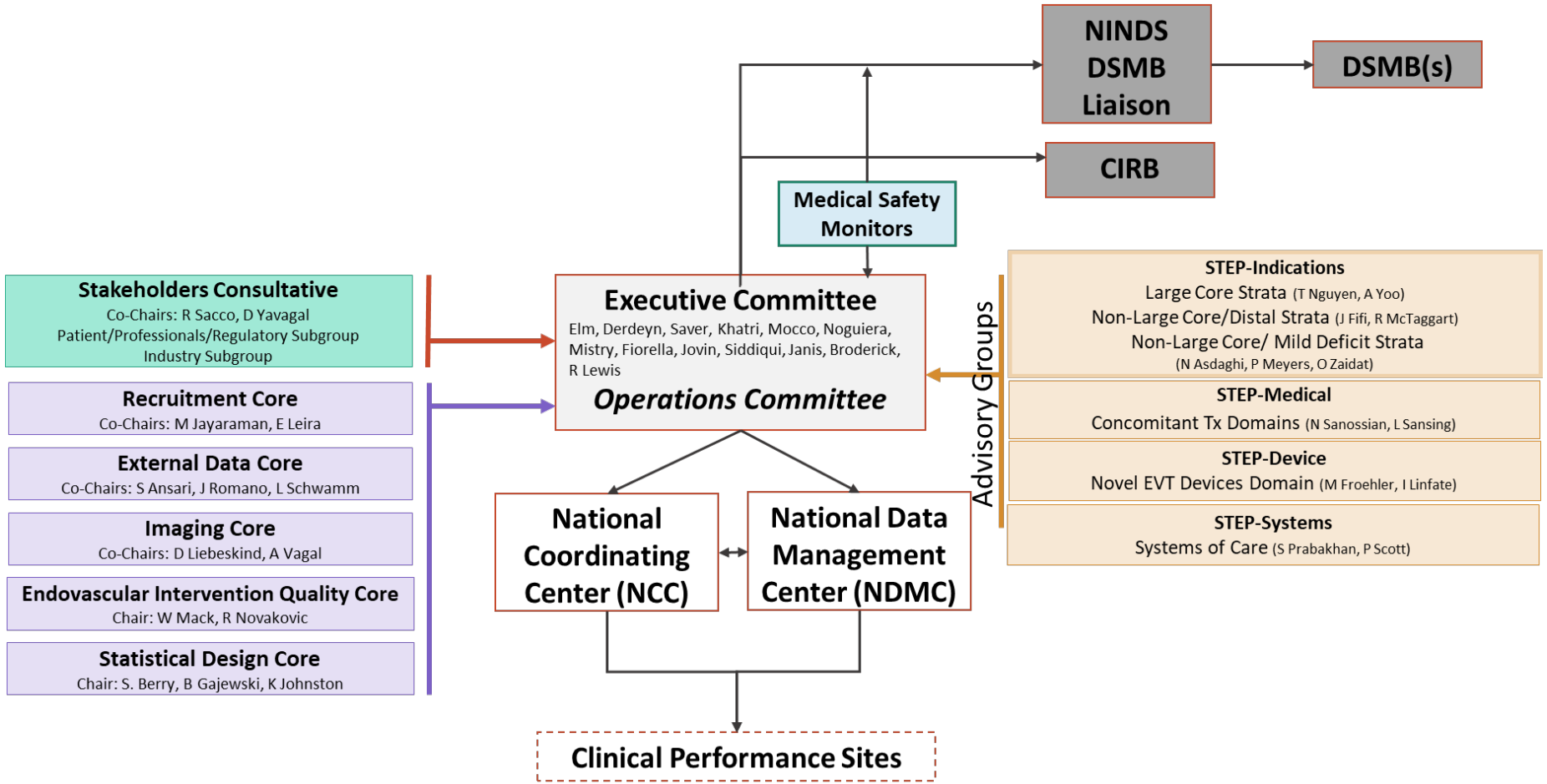
STEP Trial Domains



STEP Data Transfer Procedures

- STEP leverages three major acute stroke/endovascular registries to minimize the burden of data collection through superuser agreements
  - AHA GWTG
  - NVQI-QOD
  - SVIN registry
- Direct data entry is permissible for sites not participating in NVQI-QOD and SVIN registries.
- Direct data entry is required for critical data elements for randomized patients

STEP Organization



"We've considered every potential risk except the risks of avoiding all risks."